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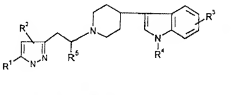
(54) Title: 1-PYRAZOL-3-YL-ETHYL-4 INDOL-3-YL-PIPERIDINE USED AS MEDICINE ACTING ON THE CENTRAL NERVOUS SYSTEM

(54) Bezeichnung: 1-(PYRAZOL-3-YL-ETHYL)-4-(INDOL-3-YL)-PIPERIDINE ALS DAS ZENTRALNERVENSYSTEM BEEINFLUSSENDE MITTEL

(57) Abstract

The invention concerns new 1-pyrazol-3-yl-ethyl-4-indol-3-piperidine derivatives of formula (I) where R^1 is H or A; R^2 is H, a phenyl substituted 1 to 3 times by Hal, NO_2, $CON(R^6)_2$, $SO_2N(R^6)_2$, cyancgen, A or R^4-O, R^3 is H, Hal, A, A-O-, amino, cyanogen, carboxamide, NO_2, $SO_2N(R^6)_2$; R^4 is H or A; A is $(C_1$-C_8alkyl or $(C_3$-C_8alkyl containing one to three times substituted by fluorine; Hal is F, Cl, Br or I. The invention also concerns the salts of said derivatives. It has been shown that these compounds have an interesting pharmaceutical activity.



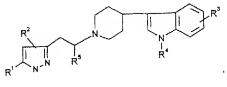
(I)

(57) Zusammenfassung

Die Erfindung betrifft neue 1-(Pyrazol-3-yl-ethyl)-4-(indol-3-yl)-piperidin-Derivate der Formel (I), worin R^1 H oder A, R^2 H, ein- bis dreifach durch Hal, NO_2, $CON(R^6)_2$, $SO_2N(R^6)_2$, Cyan, A oder R^4-O substituiertes Phenyl, R^3 H, Hal, A, A-O-, Amino, Cyan, Carboxamid, NO_2, $SO_2N(R^6)_2$, R^4 H oder A, R^5 H oder A, A Alkyl mit 1-8 C-Atomen oder ein ein- bis dreifach durch Fluor substituiertes Alkyl mit 1-8 C-Atomen, Hal F, Cl, Br oder I bedeuten, sowie deren Salze, die sich als Substanzen mit pharmazeutisch vorteilhaften Wirkungen erwiesen haben.

Abstract

The invention relates to novel 1-pyrazol-3-yl-ethyl-4-indol-3-ylpiperidine derivatives of the formula I



(I)

in which

R^1 is H or A

R^2 is H, phenyl which is mono- to trisubstituted by Hal, NO_2, $CON(R^4)_2$, $SO_2N(R^4)_2$, cyano, A or R^4-O

R^3 is H, Hal, A, A-O-, amino, cyano, carboxamide, NO_2, $SO_2N(R^4)_2$

R^4 is H or A,

R^5 is H or A,

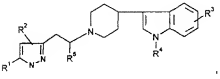
A is alkyl having 1-6 C atoms or an alkyl having 1-6 C atoms, which is mono- to trisubstituted by fluorine

Hal is F, Cl, Br or I

and their salts, which have proved to be substances having pharmaceutically advantageous actions.

1-(PYRAZOL-3-YLETHYL)-4-(INDOL-3-YL)PIPERIDINES AS COMPOSITIONS AFFECTING THE CENTRAL NERVOUS SYSTEM

The invention relates to novel 1-pyrazol-3-ylethyl-4-indol-3-ylpiperidine derivatives of the formula I



(I)

in which

R^1 is H or A

R^2 is H, phenyl which is mono- to trisubstituted by Hal, NO_2, $CON(R^4)_2$, $SO_2N(R^4)_2$, cyano, A or R^4-O

R^3 is H, Hal, A, A-O-, amino, cyano, carboxamide, NO_2, $SO_2N(R^4)_2$

R^4 is H or A,

R^5 is H or A,

A is alkyl having 1-6 C atoms or an alkyl having 1-6 C atoms, which is mono- to trisubstituted by fluorine

Hal is F, Cl, Br or I

and their salts, which have proved to be substances having pharmaceutically advantageous actions.

A large number of medicaments for the treatment of diseases which are caused by malfunctions or disorders of the central nervous system are known from the technical and patent literature. The majority of these medicaments, however, either have serious side effects or a relatively non-specific spectrum of action.

The invention was therefore based on the object of making available novel compounds which as medicaments act selectively on the central nervous system, but at the same time are low in side effects

and have no dependence potential or only a very low dependence potential.

It was also an object of the invention to make available a process whereby the appropriate compounds can be prepared in the highest possible yields and high purities.

These objects were achieved by the present invention.

It has now been found that compounds of the formula I in which the radicals R^1 - R^3, A and Hal have the meanings given, and their physiologically acceptable salts have a broad spectrum of useful pharmacological properties. They thus show, in particular, actions on the central nervous system, especially dopamine-stimulating (anti-Parkinson) and serotonin-agonistic and -antagonistic actions. Specifically, the compounds of the formula I induce contralateral pivoting behaviour in hemiparkinson rats (detectable by the method of Ungerstedt et al., Brain Res. 24, (1970), 485-493). They inhibit the binding of tritiated dopamine agonists and antagonists to striatal receptors (detectable by the method of Schwarcz et al., J. Neurochemistry 34, (1980), 772-778 and Creese et al., European J. Pharmacol. 46, (1977), 377-381) and the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol 140, (1987), 143-155). Moreover, changes in DOPA accumulation in the striatum and 5-HTP accumulation in the n. raphe occur (Seyfried et al., European J. Pharmacol. 160, (1989), 31-41). Additionally, the compounds inhibit the glossomaxillary reflex in the anaesthetized rat (detectable following the method of Barnett et al., European J. Pharmacol. 21, 81973), 178-182, and of Ilhan et al., European J. Pharmacol. 33 (1975), 61-64). Analgesic and hypotensive effects also occur; thus in catheterized conscious, spontaneously hypertensive rats (strain SHR/Okamoto/N1H-MO-CHB-Kisslegg; method cf. Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 104, (1960), 646-

648) the directly measured blood pressure after oral administration of the compounds is lowered.

The invention further relates to a process for the preparation of compounds of the given formula I and their salts, characterized in that a compound of the formula II

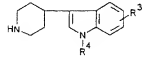
(II)

in which

R^1, R^2 and R^5 have the abovementioned meanings and

Z is Hal, $O\text{-}SO_2CH_3$, $O\text{-}SO_2CF_3$, $OSO_2\text{-}C_6H_4$ or $O\text{-}SO_2\text{-}C_6H_5$,

is reacted with a compound of the formula III



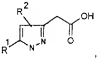
(III)

in which

R^3 and R^4 have the abovementioned meanings,

or in that

a compound of the formula IIa



(IIa)

in which

R^1 and R^2 have the meanings indicated above, is converted into an activated form, then reacted with a compound of the formula III under conditions such as are known for the formation of peptide bonds, and the

desired compound of the formula I is formed from the compound thus obtained by a reduction reaction,

and/or in that by treating with a strong base compounds of the formula I are liberated as free bases,

and/or in that a base of the formula I is converted into the associated acid addition salt using an acid.

Compounds of the formula I can have a chiral centre. Appropriate compounds of the formula I can occur in several enantiomeric forms. All these forms (e.g. D- and L-forms) and their mixtures (e.g. the DL-forms) are included in the formula I.

Above and below, the radicals or parameters R^1 to R^5, A and Hal have the meanings indicated in the formulae I to III, if not expressly stated otherwise. If several marked identically groups are present in the molecule, they can assume different definitions independently of one another.

In the above formulae, the group A has 1 to 6, preferably 1, 2, 3 or 4, C atoms. Specifically, A is preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl. The group A is furthermore a straight-chain or branched alkylene group having 1 to 6, in particular having 1 to 4 C atoms, preferably methylene or ethylene, but also, for example, ethylidene, trimethylene, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2-$, propylidene, tetramethylene, $-CH(CH_3)-(CH_2)_2-$, $-CH_2-CH(CH_3)-CH_2-$, $-(CH_2)_2-CH(CH_3)-$, $-C(CH_3)_2-CH_2-$, $-CH_2-C(CH_3)_2-$, $-CH(CH_2CH_3)-CH_2-$, $-CH_2CH(CH_2CH_3)-$, $-CH(CH_2CH_2CH_3)-$, $-C(CH_3)(CH_2CH_3)-$, $-CH(CH_3)CH(CH_3)-$ or $-CH[CH(CH_3)_2]-$. This group, however, can also be the corresponding alkyl group having 1 to 6 C atoms, which is mono- to trisubstituted by fluorine.

Accordingly, the group R^2-O-, if R^4 is A, is in particular a straight-chain or branched alkylene group having 1 to 6, in particular having 1 to 4, C atoms bonded via an oxygen atom. A-O is preferably methoxy, ethoxy, 1- or 2-propoxy, 1-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

A group designated by phenyl is preferably an unsubstituted phenyl. A substituted phenyl group is preferably monosubstituted. Such a phenyl group, however, can also be di- or trisubstituted, it being possible for the substituents to be identical or different. Preferred substituents are F, Cl, methoxy and OH. Possible substituents, however, are also NO_2, cyano, A or A-O, it being possible for A and A-O- to have the abovementioned meanings.

Specifically, a phenyl group is preferably o-, m-, p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, 2,3- 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 3-hydroxy-4-methoxyphenyl, 3-methoxy-4-hydroxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dihydroxyphenyl, 2,3- or 3,4-methylenedioxyphenyl.

Hal corresponds to a halogen radical and can be fluorine, chlorine, bromine or iodine. It is particularly preferably fluorine or chlorine.

R^1 is preferably a hydrogen or has the meanings of A.

R^2 is preferably hydrogen or a phenyl which is mono-, di- or trisubstituted by a Hal, A or R^4-O-, R^4 preferably having the meaning of A, but in particular also a phenyl mono-, di- or trisubstituted by $CON(R^4)_2$ or $SO_2N(R^4)_2$.

R^3 is preferably a hydrogen, a radical having the meaning of A, in particular methyl or ethyl, or having the meaning of R^4-O, i.e. preferably methoxy or ethoxy. Particularly preferably, it has the meaning of a cyano, carboxamido or nitro

group. In particular, it can also be an optionally substituted sulfonyl group. Possible substituents of this sulfonyl group are Hal, A, or A which is mono- to trisubstituted by Hal.

R^4 is preferably hydrogen, but can also optionally have the meanings of A, in particular it is a methyl or ethyl radical.

R^3 is, like R^4, preferably hydrogen, but can also optionally have the meanings of A, in particular it is a methyl or ethyl radical.

Among the compounds of the formula I, those are preferred in which at least one of the radicals indicated has one of the preferred meanings indicated. Some groups of preferred compounds are those of the formulae Ia to Id, which correspond to the formula I, but in which

in Ia R^1 is hydrogen or methyl;

in Ib R^1 is hydrogen or methyl and
R^2 is hydrogen or a phenyl which is mono- to trisubstituted by Hal,

in Ic R^1 is methyl and
R^3 is hydrogen, fluorine, hydroxyl, cyano, carboxamide, ethyl, methoxy or a trifluoromethylsulfonyloxy,

in Id R^1 is methyl and
R^4 is hydrogen or methyl.

The compounds of the formula I and also their starting compounds are prepared by methods known per se to the person skilled in the art, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods

of Organic Chemistry], Georg Thieme Verlag Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, but not mentioned here in greater detail.

The starting substances can, if desired, also be formed in situ, such that they are not isolated from the reaction mixture, but immediately reacted further to give the compounds of the formula I.

Starting compounds for the preparation of compounds of the formula I can be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis. Compounds of the formula I are preferably obtained by coupling reactions known to the person skilled in the art of the compounds of the formulae II or IIa with those of the formula III, if appropriate after selective hydrogenation. If possible, the synthesis of compounds of the formula I is carried out such that a solvolysis is unnecessary for the liberation of the desired compound of the formula I, especially as compounds of this structure are frequently unstable under such conditions.

Preferred starting substances for the solvolysis or hydrogenolysis are those which otherwise correspond to the abovementioned formulae, but instead of free amino and/or hydroxyl groups contain corresponding protected amino and/or hydroxyl groups, preferably those which, instead of an H atom which is bonded to an N atom, carry an amino protective group, in particular those which, instead of an HN group, carry an R'-N group in which R' is an amino protective group, and/or those which, instead of the H atom of a hydroxyl group, carry a hydroxyl protective group, e.g. those which, instead of a group -COOH, carry a group -COOR", in which R" is a hydroxyl protective group.

Several - identical or different - protected amino and/or hydroxyl groups can also be present in the molecule of the starting substance. If the protective

groups present are different from one another, in many cases they can be removed selectively.

The expression "amino protective group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at another position in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl (e.g. dinitrophenyl (DNP), aralkoxymethyl (e.g. benzoxymethyl (BOM)) or aralkyl groups (e.g. benzyl, 4-nitrobenzyl, triphenylmethyl). As the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise uncritical; however, those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" is to be interpreted in the widest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and in particular alkoxycarbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenacetyl; aroyl such as benzoyl or tolyl; aryloxyalkanoyl such as phenoxyacetyl; alkoxycarbonyl such as methyoxycarbonyl, ethoxycarbonyl; 2,2,2-trichloroethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl (BOC), 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as benzyloxycarbonyl (CBZ), 4-methoxybenzyloxycarbonyl, 9-fluorenylmethoxycarbonyl (FMOC). Preferred amino protective groups are BOC, DNP and BOM, furthermore CBZ, benzyl and acetyl.

The expression "hydroxyl protective group" is likewise generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at another position in the molecule. Typical of

such groups are unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. The nature and size of the hydroxyl protective groups is not critical, as after the desired chemical reaction or reaction sequence they are removed again; groups having 1-20, in particular 1-10, C atoms are preferred. Examples of hydroxyl protective groups are, inter alia, tert-butyl, benzyl, p-nitrobenzoyl, p-toluenesulfonyl protective groups and acetyl, benzyl and acetyl being particularly preferred.

The functional derivatives of the compounds of the formula I to be used as starting substances can be prepared by the customary methods, such as are described, for example, in the appropriate standard works and the relevant patent literature, for example by reaction of compounds which correspond to the formulae II and III, but in which at least one of these compounds carries a protective group instead of an H atom.

The liberation both of the compounds of the formulae II, IIa or III and, if appropriate, of the compounds of the formula I from their functional derivatives takes place - depending on the protective group used - e.g. with strong acids, expediently with trifluoroacetic acid or perchloroacetic acid, but also with other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid or sulfonic acids, such as benzene- or p-toluenesulfonic acid, the presence of an additional solvent is possible, but not always necessary.

Suitable inert solvents are preferably organic, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran (THF) or dioxane, amides such as dimethylformamide (DMF), furthermore also alcohols such as methanol, ethanol or isopropanol and also water. Mixtures of the abovementioned solvents are furthermore possible. Trifluoroacetic acid is preferably used in excess without addition of a further

solvent, perchloric acid in the form of a mixture of acetic acid and 70 % perchloric acid in the ratio 9:1. The reaction temperatures for the removal of protective groups are expediently between approximately 0 and 50°C; the reaction is preferably carried out between 15 and 30°C (room temperature).

The BOC group can be removed, for example, preferably using 40 % trifluoroacetic acid in dichloromethane or using approximately 3 to 5 N HCL in dioxane at 15 to 60°C, the FMOC group using an approximately 5 to 20 % solution of dimethylamine, diethylamine or piperidine in DMF at 15 to 50°C. Removal of the DNP group is carried out, for example, also using an approximately 3 to 10 % solution of 2-mercaptoethanol in DMF/water at 15 to 30°C.

Hydrogenolytically removable protective groups (e.g. BOM, CBZ or benzyl) can be removed, for example, by treating with hydrogen in the presence of a catalyst (e.g. of a noble metal catalyst such as palladium, expediently on a support such as carbon). Suitable solvents in this case are those indicated above, in particular, for example, alcohols such as methanol or ethanol or amides such as DMF. The hydrogenolysis is generally carried out at temperatures between 0 and approximately 100°C and pressures between approximately 1 and 200 bar, preferably at 20 to 30°C and 1 to 10 bar. Hydrogenolysis of the CBZ group is readily carried out, for example, on 5 to 10 % Pd-C in methanol at 20 to 30°C.

Compounds of the formula I can preferably be obtained by reaction of a pyrazole derivative of the formula II with a compound of the formula III. Use is expediently made here of the methods known per se for the N-alkylation of amines.

The leaving group Z of the formula II is preferably Cl, Br, I, C_1- to C_6-alkylsulfonyloxy, such as methane- or ethanesulfonyloxy, C_1- to C_6-fluoroalkylsulfonyloxy, such as trifluoromethanesulfonyloxy

or C_6-C_{10}-arylsulfonyloxy such as benzene-, p-toluene- or 1- or 2-naphthalenesulfonyloxy.

The reaction is carried out in an inert solvent, e.g. a halogenated hydrocarbon, such as dichloromethane, trichloromethane or carbon tetrachloride, an ether, such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile. Suitable solvents are also dimethyl sulfoxide, toluene or benzene. It is also possible, however, to use mixtures of these solvents. This reaction can be carried out at temperatures between approximately -10 and 200°C, preferably between 0 and 120°C. Preferably, the reaction is carried out in the presence of an additional base, e.g. of an alkali metal or alkaline earth metal hydroxide or carbonate such as sodium, potassium or calcium hydroxide, or sodium, potassium or calcium carbonate. If the leaving group Z is different from I, an addition of an iodide such as potassium iodide is recommended.

The starting substances of the formula II can be prepared by methods known from the literature.

The starting substances of the formula III can be prepared by methods generally known to the person skilled in the art, such as are described in handbooks on indole chemistry. As protective groups of the piperidine nitrogen, benzyl and BOC are preferred. These protective groups are particularly preferred in order to introduce a substituent designated by R^4, which is unequal to hydrogen, on the indole nitrogen. The latter reaction takes place in particular in the presence of a strong base, to be precise preferably from the group NaH, KH, $KOC(CH_3)_3$ or n-, sec- or tert-butyllithium. The removal of the "amino protective group" is then carried out according to one of the methods described above.

Starting substances of the formula IIa can be prepared by methods known from the literature, in particular analogously to the following Example 5.

Coupling reactions of compounds of the general formula IIa with compounds of the general formula III can be carried out under conditions such as are known for the formation of peptide bonds. Corresponding methods are described, for example, in "Aminosäuren, Peptide, Proteine" [Amino Acids, Peptides, Proteins], Jakubke, Hans-Dieter; Jeschkeit, Hans; Verlag Chemie, Weinheim (1982), but also in Wünsch E. (1974), "Synthese von Peptiden" [Synthesis of Peptides] in: Houben-Weyl, "Methoden der organischen Chemie" [Methods of Organic Chemistry], Vol. 15, 1/2 (Ed., Müller, E.) Georg Thieme Verlag, Stuttgart. These methods include, inter alia, the azide method, the mixed anhydride method using chlorocarbonic acid monoesters as anhydride-forming agents, various activated ester methods and the carbodiimide method, as well as its modified form, the DCC additive process. From this carbonyl compound obtained by the linkage reaction, the desired compound of the formula I can be liberated by reduction under suitable conditions.

In particular, this is carried out in the presence of a catalyst of the complex hydride group. Preferably, this reaction is carried out in a solvent from the ether group. Particularly preferably, tetrahydrofuran is used as a solvent. In general, this reduction is carried out under mild conditions at temperatures from -78 to +66°C, preferably at room temperature. In particular, this reduction can also be carried out, however, using sodium bis(2-methoxy-ethoxy)aluminium hydride (e.g. Vitride®). For this purpose, the latter is employed in excess. As solvent, in this case suitable ethers are preferred.

A base of the formula I can be converted into the associated acid addition salt using an acid. For this reaction, possible acids are in particular those which give physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as

orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, trifluoroacetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and disulfonic acids, and laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formulae I.

If desired, the free bases of the formula I can be liberated from their salts by treatment with strong bases, such as sodium or potassium hydroxide, or sodium or potassium carbonate.

As already pointed out above, the compounds of the formula I can contain one or more chiral centres and can therefore be present in racemic or in optically active form. Racemates which are obtained can be separated into the enantiomers mechanically or chemically by methods known per se. Preferably, diastereomers are formed from the racemic mixture by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the D- and L-forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as ß-camphorsulfonic acid.

Also advantageous is resolution of enantiomers with the aid of a column packed with an optically active resolving agent (e.g. dinitrobenzoylphenyl-

glycine). A suitable eluent in this connection is, for example, a mixture of hexane/isopropanol/acetonitrile.

Of course, it is also possible to obtain optically active compounds of the formula I according to the methods described above by using starting substances (e.g. those of the formula II) which are already optically active.

The novel compounds of the formula I and their physiologically acceptable salts can therefore be used as pharmaceutical active compounds for axiolytics, antidepressants, neuroleptics, anti-Parkinson agents and/or antihypertensives. They are of use for the treatment and prophylaxis of anxiety states, for the treatment of panic attacks, schizophrenia, delusional obsessions, Alzheimer's disease, migraine, anorexia, bulimia, sleep disorders and drug abuse or suitable for the control of sequelae of cerebral infarcts but also for the treatment of extrapyramidal motor side effects of neuroleptics. However, they can also be used as intermediates for the preparation of other pharmaceutical active compounds.

The compounds of the general formula I and their physiologically acceptable salts can therefore be used for the production of pharmaceutical preparations by bringing them into suitable dose form together with at least one excipient or auxiliary and, if desired, with one or more other active compounds. The preparations thus obtained can be employed as pharmaceuticals in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral or rectal) or parenteral administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, glycerol triacetate and other fatty acid glycerides, gelatin, soya lecithin, carbohydrates such as lactose or starch, magnesium stearate, talc or cellulose.

Tablets, coated tablets, capsules, syrups, juices or drops are used in particular for oral

administration. Especially of interest are coated tablets and capsules having enteric coatings or capsule shells. Suppositories are used for rectal administration and solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, for parenteral administration.

The active compounds claimed according to the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations.

The preparations indicated can be sterilized and/or contain auxiliaries such as preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants and/or flavourings. If desired, they can also contain one or more other active compounds, e.g. one or more vitamins, diuretics or anti-inflammatories.

The compounds of formula I according to the invention are generally administered in analogy to other known commercially available preparations for the indications claimed, preferably in doses between approximately 1 mg and 50 mg, in particular between 5 and 30 mg, per dose unit. The daily dose is preferably between approximately 0.02 and 20 mg/kg, in particular 0.2 and 0.4 mg/kg, of body weight.

The specific dose for each individual patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body-weight, general state of health, sex, on the diet, on the time and route of administration, on the excretion rate, pharmaceutical substance combination and severity of the particular disorder to which the therapy relates. Oral administration is preferred.

In the following, examples are given which are used to illustrate the invention, but which do not restrict the invention to the examples given.

All temperatures below are indicated in °C.

In accordance with another aspect of this invention there is provided a method for the treatment of diseases caused by malfunctions and disorders of the central nervous system which comprises administering to a subject in need of such treatment an effective amount of a compound of the formula I according to claim 1 or a salt thereof optionally in association with one or more excipients or auxiliaries.

Examples

Example 1

7-Ethyl-3-(1-benzyl-1,2,3,6-tetrahydro-4-pyridyl)indole

144 g (2.57 mol) of KOH are dissolved in 1.6 l of methanol in a 2000 ml round-bottomed flask. 120 g (approximately 0.86 mol) of 7-ethylindole and 161.4 g (approximately 0.86 mol) of 1-benzylpiperidin-4-one are then added to this solution. This reaction mixture is stirred under reflux conditions for 5 hours. A further 34.1 g (approximately 0.172 mol) of 1-benzylpiperidin-4-one are added and the mixture is stirred overnight under reflux conditions. The reaction solution obtained is concentrated in vacuo, the product being obtained in crystalline form. This crude product is recrystallized from methanol.

Yield: 224 g of 7-ethyl-3-(1-benzyl-1,2,3,6-tetrahydro-4-pyridyl)indole (~82 % of theory)

R_f 0.35 (ethyl acetate/petroleum ether 1:1)

Example 2

7-Ethyl-3-(4-piperidyl)indole

The 7-ethyl-3-(1-benzyl-1,2,3,6-tetrahydro-4-pyridyl)indole obtained from Example 1 is dissolved in a solvent mixture consisting of 2 l of methanol and 0.5 l of glacial acetic acid and hydrogenated [lacuna] in the presence of a palla-[lacuna]. The catalyst is then filtered off and the solvent is distilled off in vacuo. The residue obtained is codistilled with toluene and dissolved in 1 l of water. By the addition of sodium hydroxide solution (32 %), the pH of the solution is rendered alkaline. The crystals precipitated in this process are separated off and dried.

Yield: 153.6 g of 7-ethyl-3-(4-piperidyl)indole (~ 95 % of theory)

M.p. 189°C

Example 3

6-Methyl-2H-pyran-2,4-(3H)-dione

495 ml of sulfuric acid (90 %) are heated to 130°C in a 2 l three-necked flask. 300 g of 3-acetyl-3,4-dihydro-6-methylpyran-2,4-dione (dehydroacetic acid) are added in small portions with stirring. The mixture is then additionally stirred for some time. After reaction has taken place, the reaction mixture is poured onto approximately 1500 g of ice. The crystals formed are separated off.

Yield: 192 g of 3,4-dihydro-6-methylpyran-2,4-dione (crude product) (85 % of theory)

Example 4

2-(5-Methyl-3-pyrazolyl)acethydrazide

191.6 g of 3,4-dihydro-6-methylpyran-2,4-dione are dissolved in 800 ml of methanol. 190 g of $NH_2NH_2 \cdot H_2O$ are added dropwise to this solution with stirring, the temperature climbing to 70°C. Following the reaction, the product formed is filtered off and further processed as a crude product.

Yield: 193 g of 2-(5-methyl-3-pyrazolyl)acethydrazide (82 % of theory)

M.p.: 153-154°C

Example 5

2-(5-Methyl-3-pyrazolyl)acetic acid

105 g of 2-(5-methyl-3-pyrazolyl)acethydrazide and 720 ml of 2N sodium hydroxide solution are stirred with one another and the mixture is heated under reflux conditions for 4 hours. The reaction solution thus

obtained is then neutralized with hydrochloric acid. After this, the reaction solution is concentrated in vacuo. Crystals precipitating in the course of this are separated off and further processed directly as a crude product.

Yield: 202 g of 2-(5-methyl-3-pyrazolyl)acetic acid (crude product)

Example 6

Ethyl 2-(5-methyl-3-pyrazolyl)acetate

95 g of 2-(5-methyl-3-pyrazolyl)acetic acid and 660 g of ethanol are treated with 74 ml of thionyl chloride in a 2 l flask and stirred at room temperature for approximately 72 hours and then allowed to stand for a further 48 hours. The reaction solution is concentrated under vacuum conditions. The residue obtained is taken up in a solvent mixture consisting of ethyl acetate/methanol in the ratio 2:1, and heated under reflux conditions, the product going into solution, but not by-products and sodium chloride. The filtered mother liquor is concentrated in vacuo, the product being obtained in crystalline form.

Yield: 141 g of ethyl 2-(5-methyl-3-pyrazolyl)acetate (crude product)

Example 7

2-(5-Methyl-3-pyrazolyl)ethanol

100 g of ethyl 2-(5-methyl-3-pyrazolyl)acetate (crude product) are suspended in 2 l of ethanol. 146.6 g of $NaBH_4$ are added in portions to this suspension with stirring. This reaction mixture is stirred at room temperature for approximately 192 hours. Approximately 150 ml of water and 65 ml of glacial acetic acid are added and the ethanol is distilled off. The pasty residue obtained is taken up

in ethyl acetate and extracted several times with water. The organic phase is dried, filtered and concentrated under vacuum conditions. Further product is separated off from the aqueous phase by neutralizing and extracting with ethyl acetate.

Yield: 49 g of 2-(5-methyl-3-pyrazolyl)ethanol (~ 75 % of theory)

Example 8

2-(5-Methyl-3-pyrazolyl)ethyl chloride

49 g of 2-(5-methyl-3-pyrazolyl)ethanol are suspended in 78 ml of toluene and heated to reflux. 59.5 g of phosphorus oxychloride are added to this suspension slowly in the course of 2 hours, a strongly exothermic reaction taking place. After addition has ended, the mixture is heated under reflux for a further two hours. The reaction solution is then allowed to stand at room temperature for at least 12 hours. The pH of the solution is then adjusted to 9 using sodium carbonate and it is extracted at least three times with ethyl acetate. The combined ethyl acetate phases are dried over magnesium sulfate, the latter is filtered off and the solvent is distilled off down to dryness in vacuo. As a residue, an oil is obtained which cannot be completely crystallized. This crude product is purified by chromatography (silica gel 60; ethyl acetate/petroleum ether 9:1).

Yield: 39.4 g of 2-(5-methyl-3-pyrazolyl)ethyl chloride (~ 70 % of theory)

Example 9

7-Ethyl-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole

2.28 g (0.01 mol) of 7-ethyl-3-(4-piperidyl)-indole (Example 2) and 1.44 g (0.01 mol) of 2(5-methyl-

3-pyrazolyl)ethyl chloride (Example 8) are initially introduced into 125 ml of acetonitrile in a 250 ml round-bottomed flask [lacuna] stirred under reflux conditions for approximately 48 hours. The precipitate formed during this time is separated off. The precipitate here is unreacted starting material. The solvent of the reaction solution thus obtained is distilled off and the residue obtained is separated by chromatography (silica gel 60, ethyl acetate/methanol 3:2). After concentrating the product-containing fraction, the reaction product is precipitated as the oxalate, separated off and dried.

Yield: 1.3 g of 7-ethyl-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole oxalate (29 % of theory)

R_f: 0.28 (ethyl acetate: methanol 2:1), amorphous

Example 10

5-Fluoro-3-(1-(2-(3-(4-fluorophenyl-5-methyl-4-pyrazolyl)methylcarbonyl)-4-piperidyl)indole

2.18 g (10 mmol) of 5-fluoro-3-(4-piperidyl)-indole, 3.10 g (16 mmol) of 1-ethyl-3-(3'-dimethyl-aminopropyl)carbodiimide hydrochloride and 2.70 g (20 mmol) of 1-hydroxybenzotriazole are taken up in 100 ml of dichloromethane and the mixture is stirred for 1 hour. 2.34 g (10 mmol) of 2-(3-(6-fluorophenyl)-5-methyl-4-pyrazolyl)acetic acid are then added and the reaction solution thus obtained is stirred for approximately 72 hours. The reaction mixture thus obtained is extracted with sodium hydroxide solution and then dried over magnesium sulfate. After filtering this solution, the solvent is distilled off in vacuo. The crude product thus obtained is not worked up but directly used further in the next stage.

Yield: 6.5 g of 5-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)methylcarbonyl)-4-piperidyl)indole (crude product)

Example 11

5-Fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole

6.5 g (10 mmol) of 5-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)methylcarbonyl)-4-piperidyl)indole are dissolved in 100 ml of tetrahydrofuran and then treated with 5 ml (25 mmol) of sodium bis(2-methoxyethoxy)aluminium hydride (Vitride®). The reaction mixture thus obtained is stirred at room temperature for two hours. After reaction has ended, excess sodium bis(2-methoxyethoxy)-aluminium hydride is destroyed by addition of water, a colourless gelatinous mass forming, which is filtered off through kieselghur. The solvent is distilled off in vacuo from the reaction solution thus obtained. By this means 7.7 g of crude product are obtained, which is purified by chromatography (silica gel 60; ethyl acetate/petroleum ether 9:1).

Yield: 1.7 g of 5-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole (= 40 % of theory)

4-Fluoro-3(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole was prepared analogously.

Example 12

5-Fluoro-1-methyl-3-(1-tert-butoxycarbonyl-4-piperidyl)indole

0.9 g (30 mmol) of sodium hydride (80 %) are suspended in 300 ml of tetrahydrofuran. A solution consisting of 9.5 g of 5-fluoro-3-(1-tert-butoxy-carbonyl-4-piperidyl)indole and tetrahydrofuran is then slowly added dropwise with cooling and additionally

stirred for approximately one hour. 1.9 ml (30 mmol) of methyl iodide are then added dropwise and the mixture is additionally stirred for approximately two hours. The solution is concentrated in vacuo and the residue is taken up in ethyl acetate, extracted with water and then dried over magnesium sulfate. After filtering, it is again concentrated down to a residue in vacuo. The crude product thus obtained is purified by chromatography (silica gel 60; petroleum ether/ethyl acetate).

Yield: 6.7 g of 5-fluoro-1-methyl-3-(1-tert-butoxycarbonyl-4-piperidyl)indole (~ 67 % of theory); oil

Example 13

5-Fluoro-1-methyl-3-(4-piperidyl)indole

6.7 g (20 mmol) of 5-fluoro-1-methyl-3-(1-tert-butoxycarbonyl-4-piperidyl)indole are stirred for one hour in 150 ml of a hydrochloric acid/ether mixture (considerable evolution of gas). This solution is then concentrated in vacuo.

Yield: 5.0 g of 5-fluoro-1-methyl-3-(4-piperidyl)-indole (~ 93 % of theory)

The following compounds were prepared analogously to Example 9 or 11:

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)-indole-5-carbonitrile
M.p. 112-114°C

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)-indole-5-carboxamide
M.p. 130-131.5°C

4-fluoro-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole, R_f 0.31, ethyl ether:methanol 2:1

5-fluoro-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole, R_f 0.38, ethyl ether:methanol 2:1

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)-indole, R_f 0.40, ethyl ether:methanol 2:1

4-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole, R_f 0.52, ethyl ether:methanol 2:1

5-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole, R_f 0.53, ethyl ether:methanol 2:1

5-fluoro-1-methyl-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole, m.p. 223°C

6-fluoro-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl-4-piperidyl)indole, R_f 0.62, ethyl ether:methanol 2:1

6-methoxy-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole, R_f 0.44, ethyl ether:methanol 2:1

7-methoxy-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole, R_f 0.30, ethyl ether:methanol 2:1

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-1,2,3,6-tetra-hydro-4-pyridyl)indole-5-carbonitrile

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-1,2,3,6-tetra-hydro-4-pyridyl)indole-5-carboxamide

The following examples relate to pharmaceutical preparations:

Example A: injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogen phosphate are [sic] adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: solution

A solution of 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. The solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation.

Example D: ointment

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is

compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

Example F: coated tablets

Analogously to Example E, tablets are pressed which are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: capsules

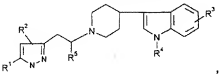
2 kg of active compound of the formula I are filled into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

Patent Claims

1. 1-Pyrazol-3-ylethyl-4-indol-3-ylpiperidine derivatives of the formula I



, (I)

in which

R^1 is H or A

R^2 is H, phenyl which is mono- to trisubstituted by Hal, NO_2, $CON(R^4)_2$, $SO_2N(R^4)_2$, cyano, A or R^4-O

R^3 is H, Hal, A, A-O-, amino, cyano, carboxamide, NO_2, $SO_2N(R^4)_2$

R^4 is H or A,

R^5 is H or A,

A is alkyl having 1-6 C atoms or an alkyl having 1-6 C atoms, which is mono- to trisubstituted by fluorine

Hal is F, Cl, Br or I

and their salts.

2. A compound according to Claim 1 selected from the group

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)-indole-5-carbonitrile,

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)-indole-5-carboxamide,

4-fluoro-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole,

5-fluoro-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole,

3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)-indole,

4-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole,

5-fluoro-3-(1-(2-(3-(4-fluorophenyl)-5-methyl-4-pyrazolyl)ethyl)-4-piperidyl)indole,

5-fluoro-1-methyl-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole,

6-fluoro-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole,

6-methoxy-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole,

7-methoxy-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole,

7-ethyl-3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-4-piperidyl)indole

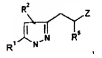
3-(1-(2-(5-methyl-3-pyrazolyl)ethyl)-1,2,3,6-tetrahydro-4-pyridyl)indole-5-carbonitrile,

3. A pharmaceutical preparation containing a compound of the general formula I according to claim 1, or at least one physiologically tolerable salt in association with a pharmaceutically acceptable excipient or auxiliary thereof.

4. A pharmaceutical preparation according to claim 3, wherein the compound of the general formula I has serotonin-agonistic and -antagonistic action.

5. A pharmaceutical preparation according to claim 3, wherein the compound of the general formula I has dopamine-stimulating action.

6. Process for the preparation of 1-pyrazol-3-ylethyl-4-indol-3-ylpiperidines of the formula I according to Claim 1 and their salts, characterized in that a compound of the formula II



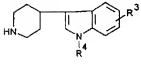
(II)

in which

R^1, R^2 and R^5 have the abovementioned meanings and

Z is Hal, $O-SO_2CH_3$, $O-SO_2CF_3$, $OSO_2-C_6H_4$ or $O-SO_2-C_6H_5$,

is reacted with a compound of the formula III



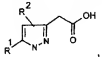
(III)

in which

R^3 and R^4 have the abovementioned meanings,

or in that

a compound of the formula IIa



(IIa)

in which

R^1 and R^2 have the meanings indicated above, is converted into an activated form, then reacted with a compound of the formula III under conditions such as are known for the formation of peptide bonds, and the desired compound of the formula I is formed from the compound thus obtained by a reduction reaction,

and/or in that by treating with a strong base compounds of the formula I are liberated as free bases,

and/or in that a base of the formula I is converted into the associated acid addition salt using an acid.

7. Process for the production of pharmaceutical preparations, characterized in that a compound of the formula I according to Claim 1 and/or one of its physiologically tolerable salts is brought into a suitable dose form together with at least one solid, liquid or semiliquid excipient or auxiliary and, if appropriate, in combination with one or more other active compounds.

8. A method for the treatment of diseases which are caused by malfunctions and disorders of the central nervous system which comprises administering to a subject in need of such treatment an effective amount of a compound of the formula I according to claim 1 or a salt thereof optionally in association with one or more excipients or auxiliaries.

9. Use of compounds of the formula I according to claim 1 or of their physiologically acceptable salts in the production of a medicament for the treatment of diseases.

10. Use according to claim 9 for the treatment of diseases which are caused by malfunctions and disorders of the central nervous system.

DATED this 30th day of November 1999

MERCK PATENT GMBH

By their Patent Attorneys
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